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Arterial Stiffness and Wave Reflections in Marathon Runners

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BACKGROUND
Regular aerobic exercise has beneficial effects on the cardiovascular system. Marathon running is an aerobic and extremely vigorous exercise. Arterial stiffness and wave reflections are independent predictors of cardiovascular risk. We investigated the acute effect of marathon race on aortic stiffness and wave reflections, as well as possible chronic alterations of these indexes in marathon runners.

METHODS
We studied 49 marathon runners (age 38 ± 9 years) and 46 recreationally active control subjects (age 37 ± 5 years). To investigate the acute effect of marathon race, a subgroup of 20 runners was evaluated after the race as well. Aortic stiffness was evaluated with carotid–femoral pulse wave velocity (PWV) and wave reflections with augmentation index (AIx).

RESULTS
Marathon runners had significantly higher systolic, diastolic, pulse (both aortic and brachial), and mean pressures compared to controls ($P < 0.05$ for all). Marathon runners had significantly higher PWV (6.89 m/s vs. 6.33 m/s, $P < 0.01$), whereas there was no difference in AIx and AIx corrected for heart rate (AIx@75) compared to controls (13.8% vs. 13.9%, $P = 0.985$ and 8.2% vs. 10.3%, $P = 0.340$, respectively). Marathon race caused a significant fall in both AIx (12.2% vs. −5.8%, $P < 0.001$) and AIx@75 (7.0% vs. 0.0%, $P = 0.01$), whereas PWV did not change significantly (6.66 m/s vs. 6.74 m/s, $P = 0.690$). Aortic and brachial systolic, diastolic, and mean pressures were also decreased ($P < 0.05$).

CONCLUSIONS
A significant fall in wave reflections was observed after marathon race, whereas aortic stiffness was not altered. Moreover, marathon runners have increased aortic stiffness and pressures, whereas wave reflections indexes do not differ compared to controls.

Keywords: *arterial stiffness; augmentation index; blood pressure; exercise; hypertension; marathon; pulse wave velocity; wave reflections*

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The protective effect of physical activity on cardiovascular system is well recognized.[1] Regular moderate-intensity exercise can reduce coronary heart disease risk through many mechanisms including modification of risk factors.[2,3] However, an increased coronary heart disease risk in individuals performing excessive exercise has been recently reported.[4–6] Marathon running is associated with high prevalence of coronary atherosclerosis[4] and myocardial damage in presumably healthy marathon runners.[7]

Aortic stiffness and wave reflections are markers of cardiovascular disease and independent powerful predictors of the corresponding risk for cardiovascular events.[8,9] Several studies have investigated the acute and long-term effect of exercise on arterial stiffness and wave reflections.[10] Acute effects include a transient increase in aortic stiffness during exercise[11,12] and a decrease in wave reflections.[11,13] In the chronic setting, subjects performing recreational exercise[2,14] and endurance training,[14–19] including ultra-endurance competitive athletes,[20] have reduced arterial stiffness[14–17,19] and lower wave reflection indexes,[15,18,20] while findings of studies on strength-trained athletes results point toward an increase of arterial stiffness.[16,21]

The marathon race is an aerobic, extremely vigorous, and competitive exercise that requires intense regular training. Acute effects of marathon race on arterial stiffness and wave reflections, as well as chronic alterations of these parameters in marathon runners, have not been elucidated. For this purpose, we compared marathon runners with matched, recreationally active controls; furthermore, we studied marathon runners before and after the race.

METHODS

Study population. The study population comprised 49 marathon runners (42 males, mean age 38 ± 9 years, regularly trained 14.97 ± 3.67 h/week for 11.6 ± 9.1 years) who participated in the 26th Athens Classic Marathon and 46 recreationally active control subjects (40 males, mean age 37 ± 5 years). All

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marathon runners included in our study performed resistance training 1 or 2 days a week, in parallel with their aerobic training, up to 1 month before the marathon. All of them maintained their normal aerobic training schedule up to 4–5 days before the race, followed by a period without training, up to the day before the race, when most of them ran at a slow pace for 10–15 min. Controls were retrieved from our Peripheral Vessels Unit database. A subject was considered recreationally active if he/she performed some kind of aerobic exercise (e.g., jogging, running, cycling) for <3 h/week. Controls were frequency matched for gender, age, height, and traditional cardiovascular risk factors. All athletes were studied 1 day before their participation in the race. To investigate the acute effect of marathon race, a subgroup consisting of 20 marathon runners (16 males, mean age 36 ± 10 years, regular training 13.99 ± 2.48 h/week for 12.4 ± 7.4 years) was chosen based on their consent before the marathon race to be evaluated after the race as well. At study entry, a questionnaire assessing personal and family medical history, lifestyle and physical activity/training habits was completed. None of the subjects had overt cardiovascular disease according to medical history, and clinical and electrocardiographic evaluation.

Study design. Subjects had fasted for at least 6 h and had abstained from caffeine, ethanol, and flavonoid-containing beverages intake for at least 12 h before the baseline measurement. Regarding the marathon runners baseline measurements took place 1 day before the race. In the acute study, the same measurements were repeated within 10–15 min after finishing the race. The study complies with the Declaration of Helsinki. The study protocol was approved by our Institutional Research Ethics Committee and all subjects provided informed consent.

Evaluation of aortic elastic properties. Pulse travels at a higher velocity in a stiff aorta. Carotid–femoral pulse wave velocity (PWV), an established index of aortic stiffness[8,22] was calculated from measurements of pulse transit time and the distance traveled between two recording sites (PWV equals distance in meters divided by transit time in seconds) with a validated noninvasive device (Complior; Artech Medical, Pantin, France), as previously described.[9] Distance was defined as the distance from the suprasternic notch to femoral artery minus the distance from the carotid artery to the suprasternic notch.

Measurement of wave reflection indexes. Central (aortic) blood pressures and augmentation index (AIx), a composite index of wave reflections and arterial stiffness, were calculated using a validated, commercially available system (SphygmoCor; AtCor Medical, Sydney, Australia), which employs the principle of applanation tonometry, as previously described.[8,9] In brief, from radial artery recordings, the central blood pressure was derived with the use of a generalized transfer function, which is an accurate estimate of the central arterial pressure waveform. Waveforms of radial pressure were calibrated according to sphygmomanometric systolic and diastolic blood pressures measured in the brachial artery. Augmented pressure is the pressure added to the incident wave by the returning reflected one and represents the pressure boost with which the left ventricle must cope at systole. AIx was calculated as the augmented pressure divided by pulse pressure and was expressed as a percentage. AIx corrected for heart rate at a heart rate of 75 beats/min (AIx@75) was also calculated. The subendocardial viability ratio (SEVR), an index of coronary artery perfusion, was defined as the ratio of the diastolic to systolic pressure—time integral expressed as a percentage.

Statistical analysis. Data were analyzed using SPSS, 10.1 (SPSS, Chicago, IL). Continuous variables are expressed as means ± s.d. Normality was tested by the Kolmogorov–Smirnov criterion. Comparison of continuous parameters was made by unpaired Student's *t*-test. The association of categorical clinical variables was assessed by the χ^2 test. Heart rate was significantly lower in marathon runners, and because SEVR is heart rate dependent, comparison of SEVR between groups was made using analysis of covariance with heart rate as the covariate. Pressures were significantly higher in marathon runners, and as PWV is pressure dependent, comparison of PWV was made using analysis of covariance (with mean blood pressure as the covariate). Multivariable linear regression analysis using a stepwise model was applied to evaluate the association between PWV as the dependent variable and the intensity of exercise (min/day), as the independent variable, after adjustment for potential confounders (age, sex, mean blood pressure, body mass index, and history of dyslipidemia). Logarithm of the intensity of the exercise was calculated in order to obtain normal distribution. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Marathon runners vs. control subjects

Demographic and clinical characteristics of the study groups are shown in **Table 1**. Marathon runners had significantly higher systolic (both aortic and brachial), diastolic (both aortic and brachial), pulse (both aortic and brachial), and mean pressure compared to controls. Marathon athletes had reduced heart rate compared to controls. Furthermore, marathon athletes had significantly higher PWV. This difference was attenuated after adjustment for mean blood pressure ($P = 0.379$), implying that it is, at least partially, pressure dependent. There was no difference in AIx and AIx@75 between the two groups. Moreover, SEVR was significantly higher in marathon runners (**Table 1**), however, this difference did not remain significant after adjusting for heart rate ($P = 0.931$). In univariable analysis, years of exercise were associated with aortic pulse pressure ($r = 0.304$, $P = 0.045$) and AIx ($r = 0.388$, $P = 0.009$) in marathon runners. Multivariable regression analysis showed that mean pressure and intensity of exercise were independent determinants of PWV (**Table 2**).

Acute effect of marathon race

Demographic and clinical characteristics of the subgroup participating in the acute study are shown in **Table 3**. Marathon

Table 1 | Baseline characteristics of the two groups (marathon, control, *N* = 95)

	Marathon (*n* = 49)	Control (*n* = 46)	*P* value
Men (%)	86	87	
Age (years)	38 ± 9	37 ± 5	0.598
Height (cm)	176 ± 7	176 ± 9	0.934
Weight (kg)	72 ± 9	74 ± 10	0.409
Body mass index (kg/m^2)	23.4 ± 2	23.7 ± 1.7	0.293
Exercise training time (h/week)	14.97 ± 3.67	—	
Duration of training (years)	11.6 ± 9.1	—	
Brachial systolic pressure (mm Hg)	126 ± 15	115 ± 12	0.000
Brachial diastolic pressure (mm Hg)	78 ± 10	71 ± 9	0.000
Brachial pulse pressure (mm Hg)	48 ± 9	44 ± 8	0.023
Mean pressure (mm Hg)	94 ± 12	86 ± 10	0.001
Aortic systolic pressure (mm Hg)	113 ± 15	102 ± 11	0.000
Aortic diastolic pressure (mm Hg)	79 ± 10	72 ± 9	0.000
Aortic pulse pressure (mm Hg)	34 ± 7	31 ± 7	0.044
Pulse pressure amplification	1.44 ± 0.17	1.46 ± 0.15	0.668
Heart rate (bpm)	60 ± 10	66 ± 8	0.005
AIx (%)	13.8 ± 12.2	13.9 ± 9.8	0.985
AIx@75 (%)	8.2 ± 12.2	10.3 ± 9.5	0.340
PWV (m/s)	6.89 ± 1.00	6.33 ± 1.03	0.008
Tr (ms)	157.98 ± 15.45	157.4 ± 15.88	0.858
SEVR (%)	181.0 ± 49.3	159.4 ± 27.0	0.023
Risk factors, *n* (%)			
Smoking	2 (4.08%)	6 (13.04%)	0.122
Hypertension	—	—	
Dyslipidemia	2 (4.08%)	4 (8.69%)	0.360
Diabetes	—	—	

For continuous variables, data are mean ± s.d. For categorical variables, data are relative frequencies (percentages).
AIx, Augmentation index; AIx@75, AIx corrected for heart rate at a heart rate of 75 bpm; bpm, beats per minute; PWV, carotid–femoral pulse wave velocity; SEVR, subendocardial viability ratio; Tr, time to wave reflection.

Table 2 | Multiple regression model evaluating the association of PWV with the intensity of exercise

	Unstandardized coefficient	Standardized coefficient	*P* value
Model (dependent variable: PWV) adjusted $R^2 = 0.293$			
Mean pressure (mm Hg)	0.043	0.507	<0.001
Exercise intensity (log (min/day))	10.375	0.247	<0.05

PWV, carotid–femoral pulse wave velocity.

Table 3 | Demographic characteristics of the study subjects participating in the acute study (*n* = 20)

Men (%)	80
Age (years)	36 ± 10
Height (cm)	175 ± 6
Weight (kg)	71 ± 8
Body mass index (kg/m^2)	23.2 ± 1.8
Waist (cm)	81.6 ± 6.7
Hip (cm)	80.7 ± 9.2
Exercise training time (h/week)	13.99 ± 2.48
Duration of training (years)	12.4 ± 7.4
Risk factors, *n* (%)	
Smoking	—
Hypertension	—
Dyslipidemia	—
Diabetes	—
Family history of CVD	4/20 (20%)

For continuous variables, data are mean ± s.d. For categorical variables data are relative frequencies (percentages).
CVD, cardiovascular disease.

race caused a significant fall in AIx, AIx@75, and SEVR (Table 4). Systolic brachial and aortic pressures, diastolic brachial and aortic pressures, and mean pressure were also decreased, whereas heart rate was significantly increased after the marathon race. PWV did not differ before and after the marathon race (Table 4).

DISCUSSION

This is the first study, to the best of our knowledge, to investigate both the acute effects of marathon race on arterial stiffness and wave reflections, and the chronic alterations of these parameters in marathon runners. Marathon race was accompanied with a significant fall in wave reflections indexes, whereas aortic stiffness was not altered. At resting conditions, marathon runners have increased aortic stiffness and pressures, whereas wave reflections indexes do not differ compared to controls. Some of the findings of this study are in line with previous observations on athletes performing endurance training; however, other findings, although seemingly unexpected according to previous knowledge, deserve further consideration and may have important clinical implications.

Chronic effects

Subjects performing recreational exercise[2,14] and endurance athletes,[14–19] including ultra-endurance competitive ones,[20] have reduced arterial stiffness[14–17,19] and lower wave reflection indexes.[15,18,20] The marathon race is an aerobic, extremely vigorous, and competitive exercise that requires intense regular training. Our finding of increased PWV and unaltered wave reflections indicates that exercise may have an inverted U-shape relation with arterial stiffness. Although effects of exercise are mainly beneficial, this effect may be detrimental beyond a

Table 4 | Aortic stiffness and central hemodynamics before and after marathon race

	Before marathon race	After marathon race	*P* value
Brachial systolic pressure (mm Hg)	127 ± 16	122 ± 11	0.012
Brachial diastolic pressure (mm Hg)	78 ± 12	70 ± 8	0.006
Brachial pulse pressure (mm Hg)	49 ± 8	52 ± 8	0.129
Mean pressure (mm Hg)	94 ± 14	85 ± 9	0.003
Aortic systolic pressure (mm Hg)	113 ± 16	102 ± 10	0.001
Aortic diastolic pressure (mm Hg)	79 ± 12	73 ± 8	0.034
Aortic pulse pressure (mm Hg)	34 ± 7	30 ± 5	0.007
Pulse pressure amplification	1.45 ± 0.15	1.75 ± 0.11	0.000
Heart rate (bpm)	62 ± 9	90 ± 9	0.000
AIx (%)	12.2 ± 12.5	−5.8 ± 11.1	0.000
AIx@75 (%)	7.0 ± 13.3	0.0 ± 10.9	0.010
PWV (m/s)	6.66 ± 0.91	6.74 ± 1.22	0.690
Tr (ms)	161.7 ± 18.6	158.2 ± 20.3	0.418
SEVR (%)	177.6 ± 55.8	98.2 ± 17.7	0.000

For continuous variables, data are mean ± s.d.
AIx, augmentation index; AIx@75, AIx corrected for heart rate at a heart rate of 75 bpm; bpm, beats per minute; PWV, carotid–femoral pulse wave velocity; SEVR, subendocardial viability ratio; Tr, time to wave reflection.

certain point. Importantly, aortic stiffness is an independent marker of coronary and extra-coronary atherosclerosis and a powerful predictor of coronary events and all-cause mortality in various population groups.[9] Although an extrapolation at this stage, increased arterial stiffness in marathon runners may be a contributing factor for the high prevalence of coronary atherosclerosis[4,23] and myocardial damage[7] that has been reported in these kinds of athletes. Interestingly, increased aortic stiffness, as well as low heart rate, could partially explain the pathophysiological link between blood pressure and left ventricular mass in marathon runners with normal blood pressure resting values.[9,24,25]

Mechanisms that may explain increased aortic stiffness are several. Repeated and, particularly, excessive stress (partially due to lower heart rate and resultant increased stroke volume and aortic distension) imposed on the elastic elements of the aortic wall may lead to their mechanical fatigue.[26] An interesting finding that corroborates this explanation is that the intensity of exercise (min/day) was an independent determinant of increased aortic stiffness in our population. Other plausible mechanisms include increased inflammatory state that has been observed in marathon runners after the race[27–29] and has been shown to unfavorably affect arterial stiffness.[30–32] Furthermore, increased oxidative stress, as it has been shown in endurance and ultra-endurance athletes,[6,33–35] may have a contributing role.[36] Data on the potential role of the endothelium are not conclusive. Although endothelial function is impaired in marathon runners after the race,[37,38] endothelial progenitor cells seem to remain unchanged.[29] Lingering sympathetic adrenergic vasoconstrictor tone[39] because of elevated circulating catecholamine levels could contribute to the increase in aortic stiffness.[40]

Acute effects

Our findings regarding the changes immediately after the marathon race may represent adaptive responses of the cardiovascular system to the demands of exercise. Decrease in wave reflections, which is in accordance with the findings of other studies,[11] is most likely due to peripheral vasodilation of muscular arteries and arterioles. Increased heart rate may have contributed in the numerical decrease of AIx, but it should be noted that changes were significant also for the AIx@75. Timing of the merging of the reflected waves with the incident wave does not appear to have an effect on changes of wave reflection indexes as PWV and time to wave reflection were not altered after the marathon race. However, it is of interest that in previous investigations, exercise led to an acute increase in aortic stiffness in subjects who do not participate in regular exercise training for competition.[11] The higher heart rate, which reduces stroke volume, and peripheral vasodilation, which may increase stroke volume, after the race could have influenced the blood volume within the aorta and consequently the dimension and elastic properties of the aorta contributing to the lack of change in PWV values before and after the race in the marathon runners. Furthermore, as hydration state is shown to influence both arterial stiffness and wave reflections,[41,42] dehydration in marathon runners after the race may have partially affected our measurements; however, the exact underlying mechanisms remain to be investigated.

Taken together these findings may imply that the aortas of marathon runners or of other frequently trained athletes accommodate better the increased cardiovascular demands during exercise compared to untrained subjects. However, this intriguing hypothesis deserves further investigation.

Specific comments—limitations

Biochemical parameters, such as lipids, that have been shown to affect the association between exercise and arterial function[43] were not measured in our study. Furthermore, $VO_{2\,max}$ measurement could have provided more information on the level of cardiorespiratory fitness of our participants.

Further insights, such as a possible U-shaped relationship of the effect of exercise on arterial stiffness and the relationship between parameters of intensity of exercise (running speed, maximum heart rate) and arterial function should be obtained in future studies. Likewise, a possible differential effect of sex on our results that could not be inferred from our study due to the sex distribution in our population should be addressed in future studies.

Both increased chronic[44] and acute[45] consumption of carbohydrates decrease AIx. Thus, chronic carbohydrate loading of marathon runners and acute ingestion of sports drinks

containing carbohydrates during the race might have affected some of our measured parameters.

In conclusion, this is the first study, to the best of our knowledge, to demonstrate that marathon race is followed by a significant fall in wave reflections indexes, whereas aortic stiffness is not altered. Moreover, marathon runners have increased aortic stiffness and pressures, whereas wave reflections indices do not differ compared to controls. These findings could contribute to a better understanding of cardiovascular performance under extreme exercise conditions and to further determine cardiovascular risk in marathon runners.

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